PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 MAR 2005
Applicant's or agent's file reference 1368-8 PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/00423	09 January 2004 (09.01.2004)	17 January 2003 (17.01.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C12Q 1/68 and US Cl.: 435/6

Applicant

PTC THERAPEUTICS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Alexandria, Virginia 22313-1450
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Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/00423

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☒ in written format

      ☒ in computer readable form

   c. time of filing/furnishing

      ☒ contained in international application as filed.

      ☒ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 35-39

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☒ the claims, or said claims Nos. 35-39 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer-readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/00423

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	18-30, 32, 34	YES
	Claims	1-17, 31, 33	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-34	NO
Industrial applicability (IA)	Claims	1-34	YES
	Claims	NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-17, 31, and 33 lack novelty under PCT Article 33(2) as being anticipated by OBOKATA ET AL.

OBOKATA ET AL teach a method of screening a potential translational regulatory element of mRNA comprising the steps of synthesizing mRNAs with random oligonucleotide sequences introduced into UTRs, and selecting mRNAs with altered translation efficiency by virtue of the inserted motifs (abstract). The process is done using translation extracts in vitro and comprise preincubating the extract with the test sequence and/or reporter RNA. The randomized sequences can be from any sequence, which reads on corresponding to a sequence from a UTR, coding region, and from any gene, including those involved in pathogenesis such as oncogenes (pages 3-4). The reporter RNA is taught as being GUS (beta-glucoronidase) and enzymatic activity is measured for the signal resulting from gene expression (enzymatic activity measured as incorporation of S35 into the protein (Examples 1-3). The extract used comprises amino acids and the entire mixture used in the method comprises a cytoplasmic translation extract, an RNA regulatory sequence which inhibits or increases translation, and a reporter mRNA.

Claims 18-30, 32, and 34 lack an inventive step under PCT Article 33(3) as being obvious over OBOKATA ET AL in view of WOOD.

OBOKATA ET AL teach a method of screening a potential translational regulatory element of mRNA comprising the steps of synthesizing mRNAs with random oligonucleotide sequences introduced into UTRs, and selecting mRNAs with altered translation efficiency by virtue of the inserted motifs (abstract). The process is done using translation extracts in vitro and comprise preincubating the extract with the test sequence and/or reporter RNA. The randomized sequences can be from any sequence, which reads on corresponding to a sequence from a UTR, coding region, and from any gene, including those involved in pathogenesis such as oncogenes (pages 3-4). The reporter RNA is taught as being GUS (beta-glucoronidase) and enzymatic activity is measured for the signal resulting from gene expression (enzymatic activity measured as incorporation of S35 into the protein (Examples 1-3). The extract used comprises amino acids and the entire mixture used in the method comprises a cytoplasmic translation extract, an RNA regulatory sequence which inhibits or increases translation, and a reporter mRNA.

OBOKATA ET AL do not specifically teach use of the screening method for identifying a test compound that modulates the translational regulatory element.

WOOD teach that another type of sample which can be assayed for the presence of luciferase is an extract of cells in which expression of the luciferase occurs in response of translation of RNA encoding the luciferase. Such uses of luciferases are of value in molecular biology and biomedicine and can be employed, for example, in screening compounds for therapeutic activity (column 9, lines 32-47).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to alter the screening method taught by OBOKATA ET AL by substituting the reporter gene with the luciferase gene taught by WOOD and using the system to test for compounds that affect the translational regulation by the translational regulatory element in the assay because WOOD teaches that

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

luciferase RNA can be used for such purpose in an extract and OBOKATA ET AL teach an extract used to assay for translation effects. One would have been motivated to do so for the expected benefit of identifying test compounds that affect translation, potentially useful in molecular biology and biomedicine as taught by WOOD.

Claims 1-34 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.